

Exhibit 20 (part 1)

Exhibit 20 (part 1)



Advancing Medical Innovation for a Healthier America

Executive Summary

July 2015



BIPARTISAN POLICY CENTER

Leadership

Senator William H. Frist, MD, Co-Chair

Former U.S. Senate Majority Leader
BPC Senior Fellow

Representative Bart Gordon, Co-Chair

Former Member, U.S. House of Representatives

Advisory Committee

Marc Boutin, JD

Chief Executive Officer
National Health Council

Mark McClellan, MD, PhD

Senior Fellow and Director, Health Care Innovation and Value Initiatives
Center for Health Policy, Brookings Institution

Patrick Soon-Shiong, MD

Chairman and Chief Executive Officer
Institute for Advanced Health

Staff

G. William Hoagland

Senior Vice President
Bipartisan Policy Center

Janet M. Marchibroda

Director, Health Innovation Initiative and
Executive Director, CEO Council on Health and Innovation
Bipartisan Policy Center

Tim Swope

Senior Policy Analyst
Bipartisan Policy Center

Sam Watters

Administrative Assistant
Bipartisan Policy Center

Eric Caplan, PhD

Independent Consultant

Gregory W. Daniel, PhD, MPH

Fellow and Managing Director
Center for Health Policy
Brookings Institution

Erin Ingraham Rogus

Policy Assistant
Office of Senator William H. Frist, MD

Julie Cantor-Weinberg

Independent Consultant

ABOUT THE INITIATIVE ON FDA: ADVANCING MEDICAL INNOVATION

The Bipartisan Policy Center's initiative on FDA: Advancing Medical Innovation is developing viable policy options to advance medical innovation and reduce the time and cost associated with the discovery, development, and delivery of safe and effective drugs and devices for patients in the United States. Former Senate Majority Leader William H. Frist, MD and former U.S. Representative Bart Gordon co-chair this initiative. The advisory committee members of the initiative are Marc Boutin, JD, CEO, National Health Council; Mark McClellan, MD, PhD, senior Fellow and director, Health Care Innovation and Value Initiatives, Center for Health Policy, Brookings Institution; and Patrick Soon-Shiong, MD, chairman and CEO, Institute for Advanced Health. Janet Marchibroda, BPC's Health Innovation director, serves as the staff director for the effort.

ACKNOWLEDGEMENTS

This paper was produced by the Bipartisan Policy Center (BPC) with input and guidance received from our distinguished co-chairs and advisory committee.

BPC would like to thank and acknowledge BPC staff Janet Marchibroda, Tim Swope, and Sam Watters, as well as Julie Cantor-Weinberg, Eric Caplan, Gregory W. Daniel, and Erin Ingraham Rogus for their contributions in research and writing. BPC would also like to thank Joann Donnellan, Ann Gordon, and Ashley Ridlon for their feedback and support.

Further, BPC would also like to acknowledge the broad and diverse range of experts and stakeholders who offered their expertise and feedback through one-on-one meetings, roundtable discussions, and events.

DISCLAIMER

The findings and recommendations expressed herein do not necessarily represent the views or opinions of the Bipartisan Policy Center's founders or its board of directors.

Letter from the Co-Chairs

The nation is at a turning point in modern health care. To usher in this new age of digitally-driven, personalized care, federal agencies must be equipped to keep the United States at the forefront of medical innovation. As former members of Congress, we are well aware of the ability of the government's ability to either incentivize or stifle industry growth and advancements.

One area in which the United States still has significant work to do is in finding the next generation of cures; for the 10,000 known diseases, there are only 500 treatments. How can this be changed? That is what we seek to answer in this report. Through extensive research and interviews with industry, patient groups, academia, government, and legislators, we have developed viable policy actions that Congress can take to reduce both the time and cost of developing and delivering safe and effective medical products to patients.

Our report focuses specifically on how to modernize the development of drugs and devices. This includes the activities of the Food and Drug Administration (FDA)—the regulatory agency that oversees the safety and effectiveness of medical products sold in the United States. One out of every \$4 spent by consumers each year is on an FDA-approved product, including drugs, devices, food, and tobacco. Expensive development and lengthy approval processes can slow access to new technologies; a new drug on average takes nearly \$2 billion and a decade to make it to market. With increased consumer cost-sharing, expensive drugs and devices are already becoming out of reach for many Americans. And for those facing a disease with potential life-saving treatments in trials, the clock is ticking entirely too slowly.

Thankfully, modernizing the process of discovering, developing, and delivering medical products has become a key focus for policymakers this year and we seek to add to and inform ongoing efforts.

Our recommendations focus on improving the medical product development process, improving regulatory clarity, strengthening the FDA's ability to carry out its mission, and increasing investment in medical products to address unmet and public health needs—all of which are expected to improve our nation's competitiveness in the global marketplace.

Americans cannot afford to rely on 20th century methodologies when the world is on the cutting edge of new health technologies. The hardworking FDA employees must be given the tools and support they need to succeed in this rapidly evolving field. It's time to take action to significantly advance medical innovation in the United States.



Senator William H. Frist, MD

Former U.S. Senate Majority Leader
Chair, Bipartisan Policy Center Initiative on
FDA: Advancing Medical Innovation



Representative Bart Gordon

Former Member, U.S. House of Representatives
Co-Chair, Bipartisan Policy Center Initiative on
FDA: Advancing Medical Innovation

Table of Contents

6	Introduction
10	Improving the Medical Product Development Process
14	Increasing Regulatory Clarity
17	Strengthening the FDA's Ability to Carry out its Mission
19	Increasing Investment in Medical Products to Address Unmet and Public Health Needs
21	Conclusion
22	End Notes



Introduction

The past two decades have been marked by unparalleled advances in science and technology. Public- and private-sector investment in biomedical research has exceeded \$100 billion per year over the last ten years.¹

In this century alone, the nation has witnessed a number of significant breakthroughs—most notably the recent cure for Hepatitis C, a disease that according to the U.S. Centers for Disease Control and Prevention (CDC) currently affects more than three million Americans.^{2,3} Americans have also seen advances in oncology, through new treatments based on new genetic understanding. However, even the most bullish proponents of pharmaceutical, biotechnology, and medical device innovations acknowledge that the United States has only scratched the surface when it comes to addressing unmet medical needs. Furthermore,

progress across all therapeutic domains has been inconsistent.⁴

The notable progress in oncology and virology has not been matched by similar breakthroughs in many other therapeutic areas. Few novel treatments for mood disorders and other brain-based diseases have emerged over the past several decades, despite considerable investment and the enormous impact of these diseases on patients, their loved ones, and the communities where they reside.^{5,6,7,8} A number of promising drugs and biologics developed to arrest the course of Alzheimer's disease have yielded disappointing results.^{9,10} America's wounded warriors continue to lack demonstrably effective treatments, let alone cures, for their invisible wounds.

Many substantial unmet medical needs remain and tens of millions of Americans have neither cures nor effective treatments for what ails them.

There are literally hundreds of examples, including:

- In 2015, there will be an estimated 1,658,370 new cancer cases diagnosed and 589,430 cancer deaths in the United States.¹¹
- An estimated 5.3 million Americans suffer from Alzheimer's disease.¹² It is the only disease among the top ten causes of death in the United States that cannot be prevented or cured.
- Approximately 60,000 Americans are diagnosed with Parkinson's disease each year, and this number does not reflect the thousands of cases that go undetected. An estimated seven to ten million people worldwide are living with Parkinson's disease.¹³
- Heart disease (which includes heart disease, stroke, and other cardiovascular diseases) remains the No. 1 cause of death in the United States, killing nearly 787,000 people alone in 2011.¹⁴

The personal and familial challenges generated by these diseases—and the more than 10,000 other known diseases for which fewer than 500 approved treatments exist—tell only part of the story.¹⁵

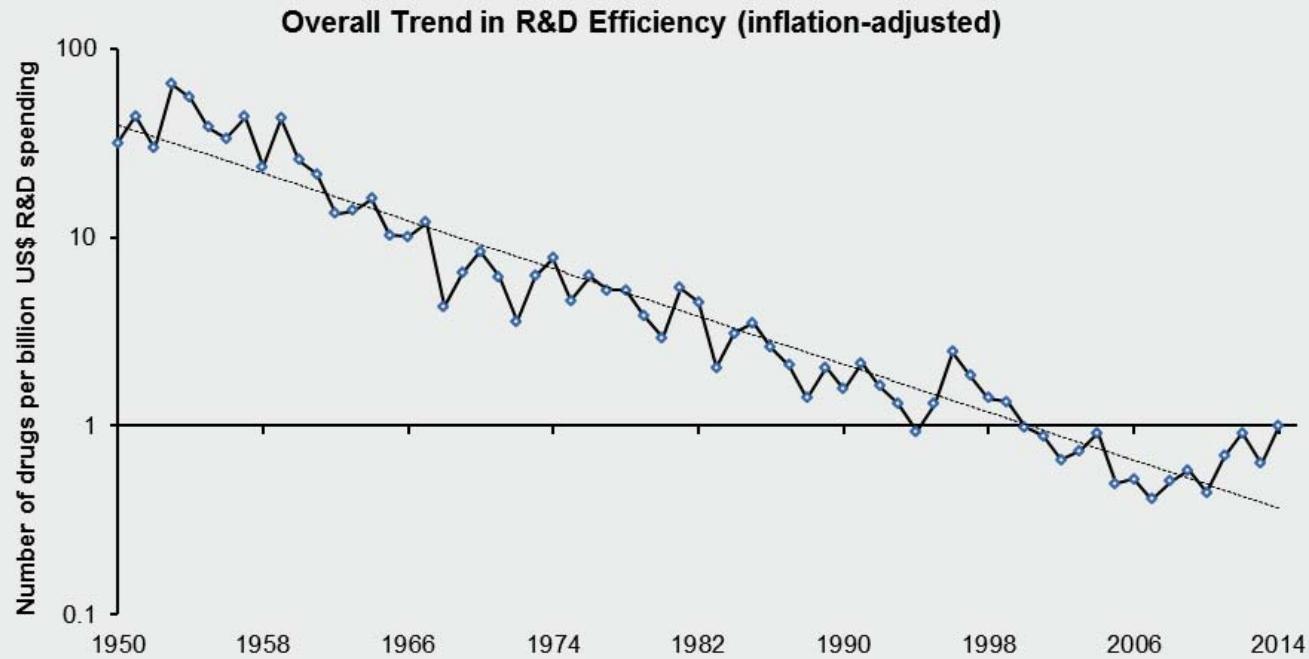
The extraordinary cost of care for those for whom neither cures nor effective treatments are available threatens to overwhelm America's social safety net and significantly constrain the capacity to address equally pressing challenges at home and abroad.

For example, Americans spend more than \$250 billion annually to care for people with Alzheimer's disease. Absent a cure or an effective treatment that alters the course of the disease, this figure is expected to exceed \$1.2 trillion by 2050.¹⁶ But that cost could be cut by a third and could reduce the number of Americans with Alzheimer's by 42 percent in 2050 by delaying the average onset

of the disease by just five years. And those figures don't even account for the benefits of alleviating the physical and emotional toll on families and loved ones; dementia caregivers had \$9.7 billion in additional health care costs of their own in 2014.¹⁷

While the United States has invested more than \$1.5 trillion in research and development (R&D) over the past two decades, it is not clear that such investments have given rise to a commensurate level of progress in the discovery, development, and approval of medical products.

Figure 1: Overall Trend in R&D Efficiency (inflation-adjusted)^{18,19}



As noted in Figure 1, the level of R&D efficiency, defined by the number of new drugs brought to the market per billion of U.S. dollars of R&D spending, has declined fairly steadily over the last 60 years.¹⁸ BPC's extension of Scannell et al's analysis of R&D efficiency shows slight improvements over the last year.¹⁹

The most reliable studies suggest it costs approximately \$2 billion and takes more than a decade to bring a new drug to market.^{20,21,22,23} The average cost of successfully launching a new molecular entity differs little between large pharmaceutical or small biotechnology companies.

Improving the efficiency of R&D and development of safe and effective medical products requires significant action on the part of academic researchers, the life sciences industry, and government

regulators throughout the phases of discovery, development, and evaluation. Congress plays a critical role in removing barriers and creating an environment that accelerates the development and delivery of safe and effective medical products.

We have identified policy actions that Congress should take to accelerate medical innovation, and reduce both the time and cost of developing and delivering safe and effective drugs and devices to patients.

It is important to note that actions associated with improving medical product discovery, such as increased federal support of biomedical research, are also needed, but are not the focus of this report.

Recommended policy actions fall into four primary areas, recommendations for which are outlined below and explained in our full report:

1. Improving the Medical Product Development Process
2. Increasing Regulatory Clarity
3. Strengthening the FDA's Ability to Carry out its Mission
4. Increasing Investment in Medical Products to Address Unmet and Public Health Needs

Together, these recommendations not only reduce the time and cost associated with the development and delivery of medical products, they are also expected to considerably increase the competitiveness of U.S. companies in the global marketplace.

This report recommends various actions that should be taken to advance medical innovation. Many of these recommendations could require additional resources not now available within the FDA's \$4.8 billion annual budget. If additional funding is required to implement the recommendations of this report, the FDA budget should be carefully reviewed and assessed to determine if current, existing programs remain priorities relative to these recommendations. If they become lower priorities, then reallocating existing resources within the FDA budget, or related health agencies' budgets should first be considered as additional resources. Second, if a net increase in funding is necessary to fund these recommendations, then additional resources should be provided through reduced federal spending from automatic spending programs (e.g. entitlements), increased user fees, revenues, or a combination of all three. The goal is to improve the health of the American public, but not at the expense of making the federal ledger less healthy.



Improving the Medical Product Development Process

1.1 Congress should accelerate the generation and use of more relevant evidence to support the development and delivery of drugs and devices, and enable assessment of the full range of factors not easily characterized in randomized clinical trials, more precise design of clinical trials, and better decision making regarding value and coverage, by performing the following:

1. Require FDA to develop a program to evaluate and prioritize the use of real-world evidence—including data from both clinical and patient experience—to support post-approval study requirements, approval of new indications for existing medical products, and ultimately improved clinical trials used for regulatory review. The FDA should engage stakeholders and experts in this process. To support this work, require FDA to develop a detailed plan within

18 months, begin implementation of a program within 24 months, and issue final guidance within 48 months.

2. Direct FDA to develop a framework for modernizing the traditional, randomized, large-scale (Phase III) clinical trials model of evidence development for regulatory review, engaging experts and stakeholders through a collaborative public process. The framework should provide an approach and regulatory requirements for incorporating data from pragmatic, randomized studies of broader populations where care is provided under more typical settings, in addition to data from randomized clinical trials.
3. Promote public- and private-sector investment in the development of a broad-based, nationwide virtual infrastructure to obtain more robust real-world evidence on both the safety and effectiveness of drugs and devices.

1.2 Congress should improve and expand the qualification and use of biomarkers to facilitate the development of safer and more effective medical products and increase the efficiency and effectiveness of the drug development process, by taking the following actions:

1. Require FDA to establish a framework and process for the submission, review, and qualification of drug development tools.
2. Authorize and strongly encourage FDA to engage with experts and stakeholders through biomedical research consortia, to support the review of qualification submissions.
3. Improve transparency of drug development tool-related activities by requiring FDA to make information regarding the number of qualification-related requests and plans submitted and the number of drug development tools qualified, publicly available.
4. Require FDA to develop—through a collaborative public process—guidance on biomarkers which contains:
 - a. A conceptual framework describing appropriate standards and scientific approaches to support development;
 - b. Recommendations for demonstrating the predictability of surrogate endpoints for purposes of supporting accelerated approval; and
 - c. Description of the requirements for entities seeking qualification, reasonable timelines for FDA review, and processes by which both entities and FDA may consult with biomedical research consortia or others with expert knowledge and insights.

1.3 Congress should improve and expand the use of patient-reported outcomes (PROs) through the following actions:

1. Require FDA to develop—through a collaborative public process—guidance on PROs that contains the following:
 - a. A standard, consistent process for submission, review, and qualification of PRO instruments;
 - b. Description of the requirements for entities seeking qualification, reasonable timelines for FDA review of submissions, and processes by which both entities and FDA may consult with biomedical research consortia or others with expert knowledge and insights; and
 - c. A conceptual framework describing appropriate standards and scientific approaches to support the development of PRO instruments.
2. Create a mechanism to improve communication between FDA and sponsors regarding the development of approaches for the use of PRO instruments.

1.4 Congress should assure the incorporation of patient perspectives into benefit-risk assessment associated with regulatory decision-making for drugs, by taking the following actions:

1. Require FDA to establish and implement a process under which an entity may submit patient preference data to enhance a structured risk-benefit framework.
2. Require FDA to publish guidance regarding process and timelines for the submission of patient preference data; methodological considerations and approaches for both collection and assessment of such data for benefit-risk; and methodologies, standards, and potential experimental designs for patient-reported outcomes.
3. To provide regulatory clarity and a predictable environment for communications, specify that the exchange of truthful and non-misleading information among patients, patient caregivers, or patient advocates and medical or scientific

staff of a manufacturer, the purpose of which is to discover and understand patient or caregiver perspectives related to the specific disease from which a patient suffers, shall not be considered promotion or commercialization of the investigational drug or biologic, or a violation of the Federal Food Drug and Cosmetic Act.

1.5 Congress should further clarify and allow increased sharing of scientific information regarding off-label use of approved medical products with health care professionals, through the following actions:

1. Require FDA to issue rules which clarify how manufacturers can disseminate truthful, non-misleading, scientific information about a drug or device that is not included in the approved labeling for the product.
2. Create a safe harbor for the dissemination of truthful and non-misleading, clinically relevant, peer-reviewed literature and other information on off-label use of drugs to health care professionals.
3. Require drug manufacturers to share data on safety and efficacy for off-label uses with researchers, regulators, and insurers, for the purpose of rapidly validating emerging uses for established therapies.

1.6 Congress should promote harmonization of international standards, through the following:

1. Require FDA to establish a clear process for recognizing standards for medical devices and require the FDA to publish guidance regarding such process.
2. Encourage FDA's commitment to and actions related to the harmonization of international standards, including, but not limited to, those related to manufacturing facilities.

3. Require FDA and the U.S. Trade Representative to report on progress on international standards harmonization.
4. Encourage FDA to participate in mechanisms that facilitate the sharing of best practices internationally.
5. Encourage FDA to explore reciprocity of approval among highly developed trading partners for well-understood drug or device classes or products for which there is high unmet medical need.

1.7 Congress should improve the interoperability of health information technology (IT) by requiring the following:

1. Require the federal government to adopt standards for health IT.
 - a. Federally adopted standards should include those required for accurate identification and matching of patient data, provider identification, transport, terminologies, clinical models, clinical data query language, security, and application interfaces.
 - b. Federal adoption should encompass inclusion of standards within certified electronic health record (EHR) technology required under the Centers for Medicare and Medicaid Services (CMS) Medicare and Medicaid EHR Incentives Programs, health IT systems procured by federal agencies, various electronic health data submissions required by federal agencies, and health IT systems directly funded through federal agency contracts, grants, and cooperative agreements.
2. To assure that federal agencies comply with federal standards, require each federal agency to report annually on its compliance with federally adopted standards and require the Government Accountability Office to issue a report, every two years, on federal compliance with such standards.

3. Designate responsibility for identification of standards for federal adoption to the Director of the Office of Management and Budget (OMB), with support from the National Coordinator for Health IT.
4. Require that any standards for federal adoption are (1) developed by a voluntary consensus body as defined by the National Technology Transfer and Advancement Act and OMB Circular A-119, (2) tested prior to adoption, and (3) established through formal rulemaking and a collaborative, public process, to assure appropriate public input and transparency.
5. Require that standards for federal adoption be published annually and that effective dates for adoption should not occur until at least 12 months subsequent to publication.
6. Authorize the Director of OMB and the National Coordinator for Health IT to use federal advisory committees to assist with the identification of areas for which standards are needed and evaluation of standards against established criteria for federal adoption, to inform federal decision-making.
7. To promote testing and validation of standards adoption and interoperability of systems, direct the National Institute of Standards and Technology (NIST) to develop and make publicly available methods for testing compliance with federal standards and authorize federal agencies to recognize independent testing and certification bodies that will provide assurance that software complies with federally adopted standards.



Increasing Regulatory Clarity

2.1 Congress should provide further clarity regarding regulatory authority associated with health IT and assure the implementation of a risk-based oversight framework for health IT that both promotes innovation and protects patient safety, by performing the following:

1. Clarify that health IT should not be subject to regulation as a medical device by the FDA, except when determined by the HHS secretary that the product poses a significant risk to patient safety.
2. Require the HHS secretary to recognize independent bodies to develop voluntary consensus standards, evaluate and render decisions on compliance with such standards, and facilitate voluntary patient safety reporting to continually improve the development, implementation, and use of health IT.

3. Clarify that current law enables those who develop and implement health IT to participate in patient safety activities and direct the HHS secretary to extend confidentiality protections to health IT developers to permit them to report patient safety events, view patient safety organization-protected information, receive and analyze patient safety event reports, create and receive quality improvement reports from patient safety organizations, and work with providers to develop strategies for improvement.

2.2 Congress should clarify regulatory authority related to laboratory-developed tests (LDTs) by performing the following:

1. Require the development of a risk-based regulatory framework for the regulation of LDTs that promotes innovation, protects patient safety, and avoids regulatory duplication.

2. Require consideration of the relevant proposals of patient, physician, industry, and laboratory stakeholders including but not limited to those of the Diagnostic Test Working Group and the College of American Pathologists, when developing the risk classification scheme.
3. Notwithstanding the FDA's October 3, 2014 draft guidance, *Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs)*, require that the framework:
 - a. Specify a risk classification for LDTs.
 - i. Risk should be defined in terms of the risk that the test produces unreliable or inaccurate information that is used to make a clinical decision; this differs from the risk posed by therapeutic devices which could cause direct bodily harm;
 - ii. Such classification should align the risk classification of an individual LDT for a given indication with the risk classification of an IVD for the same intended use; and
 - iii. Further, such classification scheme should take into account the control in place for a given LDT (i.e., the presence or absence of accreditation, proficiency tests or other means to ensure laboratory test quality).
 - b. Ensure that clinical validity information on LDTs is developed and available for each LDT;
 - c. Assure that information on diagnostic errors stemming from LDTs are available to the public (e.g., false positives and false negatives);
 - d. Leverage the information available in the existing NIH Genetic Test Registry to achieve the framework's goals; and
 - e. Address areas of overlap and regulatory uncertainty as it relates to the role of FDA and CMS through its Clinical Laboratory Improvement Amendments (CLIA) authorities.
4. Require FDA to examine its current risk classification scheme for traditional IVDs to ensure that it aligns with the unique nature of risk associated with diagnostic tests. FDA would be required to provide a report on this examination within two years to Congress. Like LDTs, IVDs do not pose risks of direct harm, in and of themselves, to patients.

2.3 Congress should improve regulatory clarity associated with precision medicine by establishing a working group that includes the FDA, the NIH, NIST, and the Office of the National Coordinator for Health IT (ONC), which would develop and submit a report to Congress. The report should characterize the rapidly evolving precision medicine landscape and develop a risk-based regulatory framework for precision medicine that protects patient safety, promotes innovation, and is flexible enough to accommodate rapid changes in science. The working group should leverage and build upon existing efforts of federal agencies, as well as the President's Precision Medicine Initiative.

2.4 Congress should improve the consistency of combination product reviews and address delays associated with the development and evaluation of combination products through the following actions:

1. Amend the Food, Drug, and Cosmetic Act to provide greater clarity regarding designation of combination products.
2. Require FDA to take actions to address the lack of coordination and agreement among collaborative centers regarding requirements, the timeliness of response, and the lack of clarity regarding data requirements.

3. Require FDA to publish a timely list of decisions to requests for designation (i.e., which FDA center has primary jurisdiction) and encourage FDA to abide by precedent when faced with a similar combination product, unless the FDA can present a rationale for making a different decision.
4. Require FDA to track and issue reports that demonstrate that milestone meetings involving sponsors and FDA are meaningfully attended by the non-lead FDA center(s), and that reviewers in non-lead centers have completed their reviews within timelines consistent with user fee performance goals of the coordinating center, e.g., the new molecular entity review model expectations and the principles outlined in the Good Review Management Practices.
3. Authorize and encourage FDA to use public-private partnerships to develop and draft guidance documents requiring significant scientific input, while leaving final approval authority with the agency.
4. Explore and address administrative barriers to finalize guidances.

2.5 Congress should improve the regulatory framework for regenerative medicine by performing the following:

1. Require FDA to provide additional clarity regarding the regulation of regenerative medicine, specifically addressing adult autologous stem cell therapy.
2. Encourage FDA's recognition of the unique nature of stem cell therapeutics, in particular autologous or similar therapies, and the fact that they require a different regulatory approach than that applied to traditional drugs or biologics. Explore the creation of a new regulatory category separate from HCT/P 351 or 361.

2.6 To improve FDA's process for creating guidances and regulations, Congress should perform the following:

1. Require FDA to seek public input on a guidance prioritization scheme.
2. Clarify that FDA should use formal rulemaking processes when making substantive policy changes.